ALKS 3831: A Novel Drug Candidate for the Treatment of Schizophrenia

Investor Presentation

MAY 10, 2018
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Introduction to ALKS 3831

ALKS 3831 Mechanism: Preclinical Observations of Olanzapine and Samidorphan
  - Central and Whole Body Effects
  - Acute and Long-Term Effects

Translational Phase 1 Metabolic Results

Clinical Results Overview
  - Phase 2 Weight and Efficacy Data
  - Phase 3 Development Program

Conclusions and Next Steps
Introduction to ALKS 3831 for Schizophrenia
ALKS 3831 for Schizophrenia

- Investigational, novel, once-daily, oral atypical antipsychotic drug candidate designed to offer robust efficacy with a favorable weight and metabolic profile
  - Administered once daily as a single, bi-layer tablet

- Differentiated mechanism of action
  - Fixed dose combination of olanzapine and a novel opioid antagonist samidorphan
    - Samidorphan included to potentially attenuate adverse metabolic sequelae of olanzapine
    - Central and peripheral effects on metabolism and weight gain in both acute and chronic settings

- Nearing completion of pivotal program
  - Beneficial weight effects demonstrated in phase 2 study
  - Antipsychotic efficacy proven in phase 3 study
  - Topline results from pivotal six-month weight study expected Q4’18
  - NDA submission planned H1 2019
Receptor Binding Activity of Antipsychotics: Drivers of Efficacy and Side Effects Difficult to Separate

ALKS 3831 Design Rationale: Retain Olanzapine’s Pharmacology Driving Efficacy and Address Metabolic Issues Through a Different System

### Olanzapine Pharmacology

<table>
<thead>
<tr>
<th>5HT&lt;sub&gt;2a&lt;/sub&gt;</th>
<th>5HT&lt;sub&gt;2c&lt;/sub&gt;</th>
<th>Musc</th>
<th>α&lt;sub&gt;1&lt;/sub&gt;</th>
<th>α&lt;sub&gt;2&lt;/sub&gt;</th>
<th>H&lt;sub&gt;1&lt;/sub&gt;</th>
<th>D&lt;sub&gt;1&lt;/sub&gt;</th>
<th>D&lt;sub&gt;2&lt;/sub&gt;</th>
<th>D&lt;sub&gt;4&lt;/sub&gt;</th>
</tr>
</thead>
</table>

### ALKS 3831 Pharmacology

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</tr>
</thead>
</table>

ALKS 3831 Mechanism: Preclinical Models Recapitulate Olanzapine-Driven Weight Gain
Samidorphan Attenuates Olanzapine-Induced Weight Gain in Female Rats

Note: All animals fed normal diet
Samidorphan Attenuates Olanzapine-Induced Weight Gain in Female Non-Human Primates (NHPs)

Note: All animals fed high fat diet
Individual data points in graph represent rolling average of previous three data points
ALKS 3831 Development Pathway

Registration

- Phase 1 POC Volunteers
- Phase 2 Efficacy + Weight N=309 Patients
- Phase 3 ENLIGHTEN-1 Efficacy N=403 Patients
- ENLIGHTEN-2 Weight N=540 Patients
- NDA for Schizophrenia

Mechanism

Preclinical
- SAM Affects OLZ-Induced Weight Gain in Animals
- What?
  - Weight / Adiposity
  - How?
    - Brain: Food Reward
    - Periphery: Metabolism

Clinical
- Acute
  - Translational Metabolism Study in Volunteers
- Chronic
  - Future Studies in Patients

ALKS 3831: Positioned for Expanded Use in Psychiatry

Mechanistic Understanding and Data
ALKS 3831 Development Pathway

**Preclinical**
- **What?**
  - Weight / Adiposity
- **How?**
  - Brain: Food Reward
  - Periphery: Metabolism

**Clinical**
- **Acute**
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**Mechanism**

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**NDA for Schizophrenia**

**SAM Affects OLZ-Induced Weight Gain in Animals**

**ALKS 3831: Positioned for Expanded Use in Psychiatry**
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**Mechanism**
- SAM Affects OLZ-Induced Weight Gain in Animals
- What?
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**Assessments:**
*Weight and body composition in rats and non-human primates*

**Future Studies in Patients**
- Mechanistic Understanding and Data
- ALKS 3831: Positioned for Expanded Use in Psychiatry

**Mechanistic Understanding in Volunteers**
- Acute Chronic Assessments:
  - Weight and body composition in rats and non-human primates
Samidorphan Attenuates Both Olanzapine-Induced Weight Gain and Increased Adiposity in Female Rats

Note: All animals fed normal diet

*OLZ vs. VEH, p<0.05
Samidorphan Attenuates Olanzapine-Induced Adiposity in Male Rats

Weight

Fat Mass

Note: All animals fed normal diet

*OLZ vs. VEH, p<0.05
Samidorphan Decreases Adiposity Accretion in Female NHPs

Weight

- VEH
- OLZ
- OLZ + SAM

Volume of Fat: Lower Pole of Kidney

Note: All animals fed high fat diet
Individual data points in graph represent rolling average of previous three data points
ALKS 3831 Development Pathway

**Phase 1**
- POC Volunteers

**Phase 2**
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  - N=309 Patients

**Phase 3**
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  - Efficacy
  - N=403 Patients
- ENLIGHTEN-2
  - Weight
  - N≈540 Patients

**Registration**
- NDA for Schizophrenia

**Mechanism**
- SAM Affects OLZ-Induced Weight Gain in Animals
- Preclinical: Weight / Adiposity
  - How?: Brain: Food Reward
  - How?: Periphery: Metabolism

**What?**
- SAM Affects OLZ-Induced Weight Gain in Animals

**How?**
- Brain: Food Reward
- Periphery: Metabolism

**Data**
- Mechanistic Understanding and Data
- Future Studies in Patients

**Future Studies**
- Clinical: Translational Metabolism Study in Volunteers
- Chronic: Future Studies in Patients

**What?**
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**Future Studies**
- Clinical: Translational Metabolism Study in Volunteers
- Chronic: Future Studies in Patients
Food Consumption Activates Reward Pathway in the Brain: Olanzapine Amplifies Normal Food Reward Pathway
ALKS 3831 Development Pathway

Registration

Phase 1 POC Volunteers

Phase 2 Efficacy + Weight
N=309 Patients

Phase 3

ENLIGHTEN-1 Efficacy
N=403 Patients

ENLIGHTEN-2 Weight
N=~540 Patients

Mechanism

SAM Affects OLZ-Induced Weight Gain in Animals

Preclinical

What?

Weight / Adiposity

How?

Brain:
Food Reward

Periphery:
Metabolism

Assessments:
Dopamine release in nucleus accumbens of female rats following high fat meal

NDA for Schizophrenia

ALKS 3831:
Positioned for Expanded Use in Psychiatry

Mechanistic Understanding and Data
Samidorphan Attenuates Olanzapine-Induced Increase in Dopamine Response to High Fat Diet in Reward Pathway in Rats

*OLZ vs. VEH, p < 0.05

*OLZ vs. OLZ + SAM, p < 0.01
ALKS 3831 Development Pathway

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**Mechanism**
- **What?**
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**Phase 2**
- ENLIGHTEN-1
  - Efficacy
  - N=403 Patients

**Phase 3**
- ENLIGHTEN-2
  - Weight
  - N=540 Patients

**ALKS 3831:**
- Positioned for Expanded Use in Psychiatry

**Preclinical**
- SAM Affects OLZ-Induced Weight Gain in Animals

**Clinical**
- Translational Metabolism Study in Volunteers
- Mechanistic Understanding and Data

**Chronic**
- Future Studies in Patients

**Acute**
- Translational Metabolism Study in Volunteers

**SAM Affects OLZ-Induced Weight Gain in Animals**
- SAM
- OLZ
- Weight Gain
- Animals

**SAM Affects OLZ-Induced Weight Gain in Animals**
Glucose Clearance Involves Insulin and Peripheral Organs: Olanzapine Disrupts Normal Process

Blood Glucose

Insulin Production

- Pancreas secretes insulin in response to increased blood glucose

Muscle
Glucose used and stored

Fat
Glucose used and stored

Liver
Glucose used, stored and released when required
ALKS 3831 Development Pathway

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**Mechanism**

**SAM Affects OLZ-Induced Weight Gain in Animals**

**Preclinical**

- **What?** Weight / Adiposity
- **How?**
  - Brain: Food Reward
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**Assessments:**
- Glucose utilization in fat and muscle
- Glucose clearance
- Insulin sensitivity

**ALKS 3831: Positioned for Expanded Use in Psychiatry**

**Mechanistic Understanding and Data**
Samidorphan Attenuates Olanzapine-Induced Disturbances in Glucose Utilization in Muscle and Fat in Female Rats

Muscle

Adipose Tissue

**VEH vs. OLZ, p < 0.001  **

*VEH vs. OLZ, p < 0.05  **OLZ vs. OLZ + SAM, p < 0.001
Samidorphan Normalizes Glucose Clearance in Female Rats When Bolus Insulin is Administered at Resting Glucose Levels

OLZ vs. VEH, p < 0.05

OLZ vs. VEH, p < 0.05
Samidorphan Prevents Hyperinsulinemia in NHPs Receiving High Fat Diet

<table>
<thead>
<tr>
<th>Pre-Study Baseline</th>
<th>DAY 28</th>
<th>DAY 58</th>
</tr>
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<tbody>
<tr>
<td>VEH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLZ+SAM</td>
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</tbody>
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Switched to OLZ + SAM at DAY 28
## Summary of Preclinical Findings and Next Steps

<table>
<thead>
<tr>
<th>Acute Effects</th>
<th>Chronic Effects</th>
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<tbody>
<tr>
<td><strong>Olanzapine</strong></td>
<td><strong>ALKS 3831</strong></td>
</tr>
<tr>
<td>Increases reward associated with food</td>
<td>Normalizes reward associated with food</td>
</tr>
<tr>
<td>Alters glucose clearance</td>
<td>Normalizes glucose clearance</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreases glucose utilization in muscle</td>
<td>Prevents and reverses hyperinsulinemia</td>
</tr>
<tr>
<td>Increases glucose utilization in fat</td>
<td>Improves glucose clearance</td>
</tr>
<tr>
<td>Decreases insulin sensitivity in liver</td>
<td>Does not restore insulin sensitivity in liver</td>
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### Future research:
- Interrogate how samidorphan normalizes glucose clearance and relationship to insulin sensitivity
- Continue to characterize the effects of olanzapine and ALKS 3831 on caloric intake and energy expenditure
- Investigate the effects of olanzapine and ALKS 3831 on circulating lipids
  - We have not observed consistent changes in lipid parameters in our preclinical studies to date
Translational Phase 1 Metabolic Study
**ALKS 3831 Development Pathway**

**Registration**
- Phase 1 POC Volunteers
- Phase 2 Efficacy + Weight N=309 Patients
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**Mechanism**
- **What?** Preclinical
  - Weight / Adiposity
- **How?**
  - Brain: Food Reward
  - Periphery: Metabolism

**Assessments:**
- Oral glucose tolerance test (OGTT)
- Mixed meal tolerance test (MMTT)
- Assessment of de novo lipogenesis
- 2-step insulinemic, euglycemic clamp procedure
- Dual energy X-ray absorptiometry measurements
- Indirect calorimetry and food intake / appetite

**Mechanistic Understanding and Data**
- **Acute** Translational Metabolism Study in Volunteers
- **Clinical**
- **Chronic** Future Studies in Patients

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Goal: Gain insights into acute metabolic effects of olanzapine and ALKS 3831
- Study designed to enable evaluation of acute metabolic effects that precede pronounced or prolonged weight gain

Study design details
- 60 healthy volunteers randomized 2:2:1 to ALKS 3831, olanzapine or placebo
  - Powered as an exploratory study (pre-specified threshold for significance p=0.10)
  - No regular exercise permitted from screening through end of treatment period
Weight Gain Profile of Olanzapine and ALKS 3831 During Initial Three Weeks of Treatment

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Placebo (N=12)</th>
<th>Olanzapine (N=24)</th>
<th>ALKS 3831 (N=24)</th>
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<tbody>
<tr>
<td>1</td>
<td>-0.0 ± 0.5</td>
<td>0.5 ± 0.5</td>
<td>-0.1 ± 0.5</td>
</tr>
<tr>
<td>8</td>
<td>0.1 ± 0.5</td>
<td>1.0 ± 0.5</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>15</td>
<td>0.3 ± 0.5</td>
<td>1.5 ± 0.5</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>22</td>
<td>0.5 ± 0.5</td>
<td>2.0 ± 0.5</td>
<td>2.5 ± 0.5</td>
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</tbody>
</table>
### Oral Glucose Tolerance Test (OGTT): Olanzapine-Induced Hyperinsulinemia Mitigated by Samidorphan

- **Ratio of AUC$_{0-3h}$ at Day 19 to Baseline**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Olanzapine</th>
<th>ALKS 3831</th>
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</thead>
<tbody>
<tr>
<td><strong>Glucose</strong></td>
<td>1.00</td>
<td>1.05†</td>
<td>1.04†</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>1.06</td>
<td>1.41†††</td>
<td>0.96</td>
</tr>
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</table>

- **Between Groups**
  - * p<0.1
  - ** p<0.01
  - *** p<0.001

- **Within Groups**
  - † p<0.1
  - †† p<0.01
  - ††† p<0.001
Mixed Meal Tolerance Test (MMTT): Replication of Olanzapine-Induced Hyperinsulinemia and Mitigation by Samidorphan

Between Groups
* p<0.1  ** p<0.01  *** p<0.001

Within Groups
† p<0.1  ‡‡ p<0.01  ‡‡‡ p<0.001
Acute Lipid Panel: Triglycerides, HDL and LDL

Between Groups
* p<0.1, ** p<0.01, *** p<0.001

Within Groups
† p<0.1, †† p<0.01, ††† p<0.001
Learnings from Metabolic Study

- Samidorphan was found to mitigate olanzapine-induced hyperinsulinemia as assessed by OGTT & MMTT
  - Normalization of glucose clearance observed despite undetectable change in insulin sensitivity using a hyperinsulinemic euglycemic clamp
  - Recapitulated what was seen preclinically

- Lipid panels uninformative due to duration and nature of acute study

- Informative for future streams of research and optimal study designs
**ALKS 3831 Development Pathway**

**Phase 1**
- POC Volunteers

**Phase 2**
- Efficacy + Weight
  - N=309 Patients

**Phase 3**
- ENLIGHTEN-1
  - Efficacy
    - N=403 Patients
- ENLIGHTEN-2
  - Weight
    - N~540 Patients

**Registration**
- NDA for Schizophrenia

**Mechanism**
- SAM Affects OLZ-Induced Weight Gain in Animals

**Preclinical**
- What?
  - Weight / Adiposity

**Brain: Food Reward**
- How?

**Periphery: Metabolism**

**Clinical**
- Acute
  - Translational Metabolism Study in Volunteers

**Chronic**
- Future Studies in Patients

**Future Studies in Patients**

**Mechanistic Understanding and Data**

**ALKS 3831: Positioned for Expanded Use in Psychiatry**

**SAM Affects OLZ-Induced Weight Gain in Animals**
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**NDA for Schizophrenia**

**ALKS 3831:** Positioned for Expanded Use in Psychiatry

**ENLIGHTEN-1**
- Efficacy
- N=403 Patients
- Acute
- Clinical
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**ENLIGHTEN-2**
- Weight
- N=~540 Patients
- Translational Metabolism Study in Volunteers
- Mechanistic Understanding and Data
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**ALKS 3831:** Positioned for Expanded Use in Psychiatry

**Clinical**
- Acute Translational Metabolism Study in Volunteers
- Chronic Future Studies in Patients

**NDA for Schizophrenia**

**Mechanistic Understanding and Data**
ALKS 3831 Phase 2 Study Assessed Efficacy and Attenuation of Olanzapine-Induced Weight Gain

- 309-patient, multicenter, double-blind, active-controlled, dose-ranging study
  - Following one-week oral olanzapine lead in, all patients randomized to olanzapine or three different doses of ALKS 3831 for 12 weeks (Stage 1)
    - Olanzapine + 5 mg, 10 mg or 20 mg samidorphan
    - Followed by 12-week extension period in which all patients received ALKS 3831 (Stage 2)

- Primary endpoint: PANSS total score at Week 12, compared to olanzapine

- Secondary endpoints focused on impact of ALKS 3831 on weight gain, compared to olanzapine
ALKS 3831 Phase 2 Study: Effect on Weight Gain

- **OLZ**
- **ALKS 3831‡ 20mg (Switch from Olanzapine/Samidorphan 0 mg)**
- **ALKS 3831†**

**Percent Change in Body Weight (LS Mean ± SE)**

- **Baseline**
- **Study Week**

Note: Analysis based on MMRM

*Switched to flex olanzapine dose plus samidorphan 20 mg

*\(p<0.05\) vs. olanzapine; **\(p<0.01\) vs. olanzapine

\(^1\)ALKS 3831 combined treatment groups

\(^2\)Switched to flex olanzapine dose plus samidorphan 20 mg

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ALKS 3831 Phase 2 Study: Antipsychotic Efficacy

Mean (±SE) PANSS Total Score

- OLZ
- ALKS 3831† 20mg (Switch from Olanzapine/Samidorphan 0 mg)
- ALKS 3831‡

†ALKS 3831 combined treatment groups
‡Switched to flex olanzapine dose plus samidorphan 20 mg

Note: Analysis based on summary statistics

Baseline 1 2 4 8 12 13 16 20 24

Study Week
Safety profile:
- AEs with a difference >5% vs. olanzapine: somnolence, sedation and dizziness; mild and transient
- Low rates of discontinuation related to AEs (5% olanzapine vs. 8% ALKS 3831)
- Low rate of serious adverse events (3% olanzapine group vs. 5% ALKS 3831)

No significant trends or changes in laboratory values, vital signs or ECG

Safety profile was consistent in both Stage 1 and Stage 2
ALKS 3831 Development Pathway

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*SAM Affects OLZ-Induced Weight Gain in Animals*

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- Acute
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*Chronic*
- Future Studies in Patients

*Mechanistic Understanding and Data*

*ALKS 3831: Positioned for Expanded Use in Psychiatry*
## ALKS 3831: Straightforward Phase 3 Program Completing in 2018

<table>
<thead>
<tr>
<th>ENLIGHTEN-1</th>
<th>Four-Week Efficacy Study</th>
</tr>
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<tbody>
<tr>
<td>- Antipsychotic efficacy vs. placebo</td>
<td></td>
</tr>
<tr>
<td>- 403 patients with acute schizophrenia</td>
<td></td>
</tr>
<tr>
<td>- ALKS 3831 demonstrated statistically significant reductions from baseline in PANSS scores, compared to placebo (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>- Olanzapine achieved similar improvements from baseline PANSS scores, compared to placebo (p=0.004)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ENLIGHTEN-2</th>
<th>Six-Month Weight Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Weight change vs. olanzapine in ~540 patients with stable schizophrenia</td>
<td></td>
</tr>
<tr>
<td>- Co-primary endpoints</td>
<td></td>
</tr>
<tr>
<td>- Percent change from baseline in body weight</td>
<td></td>
</tr>
<tr>
<td>- Proportion of subjects with ≥ 10% weight gain</td>
<td></td>
</tr>
<tr>
<td>- Data expected Q4 2018</td>
<td></td>
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</tbody>
</table>

NDA submission planned in H1 2019
ENLIGHTEN-1: ALKS 3831 Phase 3 Antipsychotic Efficacy Study
Change from Baseline in PANSS Total Score (Primary)

Change from Baseline in PANSS Total Score (Primary)

<table>
<thead>
<tr>
<th>Day</th>
<th>Change from Baseline at Week 4</th>
<th>PBO (N=112)</th>
<th>ALKS 3831 (N=124)</th>
<th>OLZ (N=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-19.4 (14.80)</td>
<td>-23.7 (12.61)</td>
<td>-22.4 (13.63)</td>
</tr>
<tr>
<td></td>
<td>LS Mean (SE)</td>
<td>-17.5 (1.32)</td>
<td>-23.9 (1.28)</td>
<td>-22.8 (1.29)</td>
</tr>
<tr>
<td></td>
<td>LS Mean Difference (SE) vs. Placebo</td>
<td>-6.4 (1.83)</td>
<td>-5.3 (1.84)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P-Value</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05
** p<0.01
*** p<0.001

Treatment Group:
- Placebo
- Olanzapine
- ALKS 3831

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ENLIGHTEN-1 Phase 3 Antipsychotic Efficacy Study: Most Common Adverse Events

<table>
<thead>
<tr>
<th>Any TEAE ≥5%</th>
<th>ALKS 3831 (n = 134) n (%)</th>
<th>OLZ (n = 133) n (%)</th>
<th>PBO (n = 134) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight increased</td>
<td>25 (18.7)</td>
<td>19 (14.3)</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>12 (9.0)</td>
<td>13 (9.8)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10 (7.5)</td>
<td>7 (5.3)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (6.0)</td>
<td>7 (5.3)</td>
<td>4 (3.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight, kg, mean (SD)</th>
<th>Baseline weight</th>
<th>Change in weight at Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALKS 3831 (n = 134)</td>
<td>77.9 (15.4)</td>
<td>3.0 (3.6)</td>
</tr>
<tr>
<td>OLZ (n = 133)</td>
<td>82.2 (19.3)</td>
<td>2.4 (3.7)</td>
</tr>
<tr>
<td>PBO (n = 134)</td>
<td>76.6 (15.9)</td>
<td>0.2 (2.8)</td>
</tr>
</tbody>
</table>

No significant trends or changes in laboratory values, vital signs or ECG
ALKS 3831 Development Pathway

**Registration**

- **Phase 1 POC Volunteers**
- **Phase 2**
  - Efficacy + Weight
  - N=309 Patients
- **Phase 3**
  - ENLIGHTEN-1
    - Efficacy
    - N=403 Patients
  - ENLIGHTEN-2
    - Weight
    - N=~540 Patients

**Mechanism**

- **Preclinical**
  - **What?**
    - Weight / Adiposity
  - **How?**
    - Brain: Food Reward
    - Periphery: Metabolism

- **Clinical**
  - Acute
    - Translational Metabolism Study in Volunteers
  - Chronic
    - Future Studies in Patients

**NDA for Schizophrenia**

**ALKS 3831: Positioned for Expanded Use in Psychiatry**

**Mechanistic Understanding and Data**
Original Hypothesis: Chronic Olanzapine Use Causes Multiple Metabolic Dysfunctions, Driven by Exaggerated Food Reward

- Olanzapine
- Food Reward
- Body Composition (± Weight Gain)
  - Dysregulation
    - Glucose
    - Insulin
    - Lipids
- Metabolic Syndrome & Diabetes
New Learnings: Chronic Olanzapine Use has Direct Effect on Body Composition, Independent of Food Reward Pathway

- Olanzapine
- Food Reward
- Body Composition (+/- Weight Gain)
- Dysregulation: Glucose, Insulin, Lipids
- Metabolic Syndrome & Diabetes
New Learnings: Olanzapine has Both Acute and Long-Term Effects on Dysregulation of Metabolic Functions
Samidorphan Disrupts Olanzapine’s Acute and Long-Term Effects

Samidorphan

Olanzapine

Food Reward

Body Composition (+/- Weight Gain)

Acute and Long-Term Dysregulation
- Glucose
- Insulin
- Lipids

Metabolic Syndrome & Diabetes
Conclusions and Next Steps

- Samidorphan plays important multifaceted role in mitigating olanzapine-induced disturbances:
  1. Food reward
  2. Glucose clearance and/or hyperinsulinemia
  3. Weight and adiposity

- Additional mechanistic research planned to further interrogate long-term effects in patients

- Pivotal development program nearing completion
  - Antipsychotic efficacy proven in phase 3 ENLIGHTEN-1 study
  - Data from ENLIGHTEN-2 six-month weight study expected Q4’18

- Planned NDA filing H1 2019
Q&A

Mark Namchuk, Ph.D., Senior Vice President of Research, Pharmaceutical and Non-Clinical Development

Craig Hopkinson, M.D., Chief Medical Officer, Senior Vice President of Medicines Development and Medical Affairs

Richard Pops, Chief Executive Officer